UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,020	01/09/2006	Irene Bozzoni	2312.001US1	7176

21186 7590 04/03/2009

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
P.O. BOX 2938
MINNEAPOLIS, MN 55402

EXAMINER	
CHONG, KIMBERLY	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
04/03/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,020	BOZZONI ET AL.	
	Examiner	Art Unit	
	KIMBERLY CHONG	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 January 2009* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/20/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 11/20/2008 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 08/18/2008 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 11/20/2008, claims 1-7 are pending and currently under examination in the application.

Information Disclosure Statement

The submission of the Information Disclosure Statement on 01/09/2009 is in compliance with 37 CFR 19.7. The information disclosure statement has been considered by the examiner and signed copies have been placed in the file.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kreutzer et al. (US 20040001811 of record cited on PTO 892 mailed 08/18/2008), Elbashir et al. (Methods 2002, Vol. 26: 199-213 of record cited on PTO 892 mailed 08/18/2008), Nilsen et al. (US Patent No. 6013447), De Young et al. (Biochemistry 1994, cited in IDS filed 11/20/2008), Hernandez (EMBO 1985, Vol. 4, No. 7: 1827-1837 of record cited on PTO 892 mailed 08/18/2008) and Skuzeski et al. (JBC 1984, Vol. 259, NO. 13: 8345-8352 of record cited on PTO 892 mailed 08/18/2008).

The instant claims are drawn to a recombinant vector for expression of a siRNA or miRNA comprising from 5' to 3' an RNA polymerase II promoter sequence from the U1 snRNA gene, suitable restricts sites for cloning, a sequence transcribing a pre-siRNA comprising an A or G residue, a sequence from 21 to 23 nucleotides corresponding to a sense region of a mRNA, a loop region, a sequence from 21 to 23 nucleotides corresponding to the antisense region, two final UU 3' overhang nucleotides and a termination sequence derived from the sequence at the 3' end of the gene for U1 snRNA, wherein the cloning site for the 5' end of the sequence is Bgl II, wherein the sequence has the structure as recited in claims 3 and 4, wherein the termination sequence is SEQ ID No. 18 as recited in claim 5 and wherein the promoter is inducible.

Kreutzer et al. teach the siRNA wherein the siRNA can be expressed from an expression vector wherein the siRNA is transcribed by promoter and expressed as an inverted repeat joined by a linker polynucleotide such that the siRNA has a stem and loop structure (see paragraph 0087). Kreutzer et al. teach the use of U1 snRNA pol II promoters, wherein the promoter is inducible (see paragraphs 0089 and 0090) and

teach pharmaceutical preparation of the siRNA expression vector for gene therapy (see paragraph 0093). Kreutzer et al. teach the use of siRNA for inhibition of expression of target genes and teach the siRNA comprising a sense and antisense strand of 19-24 nucleotides in length, preferably 21 to 23 nucleotides in length with 3' overhang regions of 1-4 nucleotides (see paragraph 0033). Kreutzer et al. do not teach siRNAs specifically comprising UU 3' overhangs, the use of termination sequences derived from the 3' end of the U1 snRNA sequence nor teach specifically a Bgl II cloning site.

Elbashir et al. teach the basic protocol for selection of siRNA sequences that can be targeted to any gene and specifically teach siRNA comprising 3' overhang regions comprising two U nucleotides (see page 202).

Nilsen et al. teach the use of an expression vector for expressing small inhibitory RNAs, such as antisense and ribozymes, comprising U1 snRNA pol II promoters and teach such expression units preferably comprise a termination sequences (see entire column 13, especially line 50-53).

De Young et al. teach the advantages of using a U1 expression vector system for expression of inhibitory molecules such as ribozymes. De Young et al. teach the use of the 3' conserved sequence (3' box) of the U1 snRNA gene as the only element required for 3' end formation and state the U1 vectors which comprise the U1 promoter and the U1 3' termination sequence can direct high levels of expression of short transcripts that are not polyadenylated (see page 12136).

The remark by De Young et al. that the 3' box is essential for formation of mature transcripts was recognized by Hernandez who teach that formation of the 3' end of

mature transcripts synthesized by a U1 snRNA RNA pol II promoter is directed by specific conserved U1 snRNA sequences located at the 3' end, which comprises the claimed termination sequence having SEQ ID No. 18 (see Figure 5).

Skuzeski et al. teach identification of essential regions of the U1 siRNA promoter that are required for transcription initiation (see Abstract). Region -105 to -6 was identified to be essential for proper initiation of transcription from the U1 promoter (see page 8351 to 8352) and in order to clone this region into an appropriate vector, the HU1-1 gene should be digested with a Bgl II enzyme which cleaves the gene at position -6 (see Figure 5 and page 8346 column 1).

It would have been obvious to one of ordinary skill in the art to make an expression vector capable of expressing a siRNA wherein the siRNA comprises 3' UU overhangs as taught by Elbashir et al. It would have further been obvious to in expressing a siRNA using a U1 expression vector as taught by Kreutzer et al. to use the elements taught by Nilson et al. and Hernandez, such as the 3' end termination sequence and further to clone the U1 snRNA promoter into the expression vector using a Bgl II restriction site for the reasons taught by Skuzeski et al.

One of ordinary skill in the art would have looked to Elbashir et al. while making a siRNA as taught by Kreutzer et al. in order to design the optimal siRNA which includes 3' UU overhangs given it was well known in the art that Elbashir et al. provides the rules for efficient construction of siRNA capable of mediating gene silencing. The limitation requiring the expression vector to have at position +1 an A or G residue would be a matter of routine design choice based on the sequence being targeted and design of the

region of the desired siRNA that needs to be complementary to the target sequence and therefore would be obvious to one of ordinary skill in the art. Further, one of ordinary skill in the art would have wanted to use a termination sequences in an expression construct given Nilsen et al. teach such sequences are preferred when constructing an expression vector to express inhibitor RNAs. One of ordinary skill in the art would have wanted to use the 3' end of a U1 snRNA promoter as a termination sequence given Hernandez teach specific conserved sequences of the 3' end of the U1 snRNA gene is required for formation of mature transcripts by a U1 snRNA promoter. The benefits of construction of expression vectors comprising U1 snRNA promoters for expression of small inhibitory RNA are well known in the art as demonstrated by the references above.

Moreover, given that is was well known in the art about the termination sequences and the essential regions required for transcription initiation using a U1 snRNA promoter, as demonstrated by Hernandez and Skuzeski et al., one would have wanted to use the required termination sequences to efficiently express the siRNAs from the vector taught by Kreutzer and one of ordinary skill in the art would have generated a Bgl II cloning site at the 5' end of a construct to efficiently be able to clone the required regions as taught by Skuzeski et al. One of ordinary skill in the art would have wanted to use a Bgl II cloning site to be able to clone in the required region to restore this region to the wild-type sequence to be able to initiate transcription of a siRNA sequence.

One of ordinary skill in the art would have expected to be able to incorporate two U nucleotides at the 3' end of the siRNA given Kreutzer et al. teach dsRNA with 3' overhangs and given Elbashir et al. teach the basic steps in designing such a siRNA sequence. One would have further expected to be able to incorporate the 3' termination sequence of the U1 snRNA gene into a construct comprising a U1 promoter because Hernandez has demonstrated this sequence works to create mature 3' end transcripts from an expression vector comprising a U1 promoter.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Although this is a new rejection, response to Applicant's arguments will be addressed as they apply to the references above.

Applicant argues that none of the references relate to the use of a U1 promoter to produce siRNA from a vector, rather each relating to siRNAs employs conventional oligonucleotide synthesis to prepare individual ssRNAs and Hernandez and Skuzeski et al. were employed to detect cis-acting elements. To the contrary, Kreutzer et al. clearly teach the preparation of siRNA using expression vectors and teach such vectors comprise promoters such as the claimed U1 promoter. With regard to Hernandez and Skuzeski et al., each of the references were cited to teach the necessary regions required when using U1 elements to produce a proper and mature transcript. One of skill in the art in using a U1 promoter in an expression vector would have clearly looked

to both Hernandez and Skuzeski et al. in constructing an efficient vector for use in gene therapy.

Applicant argues that none of the cited references disclose or suggest an expression vector which allows for the expression of a functional double-stranded molecule that can be recognized and correctly processed after transcription. Applicant's arguments are based on limitations of the invention that are not instantly claimed. The claims are drawn to recombinant vector for effective expression of a siRNA comprising a U1 promoter and termination sequences. Thus, the claimed invention as a whole would have been obvious to one of ordinary skill in the art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within

5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Kimberly Chong/
Primary Examiner
Art Unit 1635